Remarks

Amendment to the claims

Claims 1-19 are pending. Claims 1-19 are amended in response to the rejections under 35 U.S.C. 102(b) and 35 U.S.C. 103. Support for the amendment to the claims is found at p. 5, line 7 to p. 7, line 30.

Rejections under 35 U.S.C. 112

Claims 1-19 were rejected as allegedly indefinite. The applicants respectfully traverse this rejection if it is applied to the claims as amended.

Claims 1, 7 and 14 have been amended to specifically recite that the microparticles are formed of the drug and a material defined in the claims. Claims 1-19, as amended, are now clear and definite.

Rejections under 35 U.S.C. 102(b)

Claims 1-4, 6-11, 13-17 and 19 were rejected as anticipated under 35 U.S.C. 102(b) by U.S. Patent No. 5,690,954 to Illum ("Illum"). The applicants respectfully traverse the rejection if it is applied to the claims as amended.

The claimed invention

Claims 1-19, as amended, are drawn to a composition for the nasal administration of a drug in a dry powder form having an average particle size of between 10 and 20 microns, in a dosage formulation suitable for administration to the nasal region and a method of using the composition. The dry powder form contains microparticles comprising the drug and a material which can be a diketopiperazine or a polymer defined therein. A critical aspect of the formulation is the range of its particle size between 10 and 20 microns (p. 2, lines 19-23). A size

below 10 microns would cause the composition to pass into the pulmonary regi n or mouth, which would result in a low efficient delivery of the drug and cause undesirable of certain type of drugs, e.g., bitterness of an antihistamine. A size range in the range between 10 microns and 20 microns allows a lower dosage to be administered, avoids or ameliorates the systemic side effects such as somnolescence due to lower dosage, and avoids the problem with bitter taste for drugs such as antihistamine (p. 2, lines 2-16).

Illum

Illum describes a drug delivery system including a plurality of microsphere particles containing an active drug and including a material associated with each particle (col. 4, lines 5-12). The material has the property of increasing the bioavailability of the drug and can be phospholipids and lysophosphatidyl compounds (col. 4, lines 22-30). The microspheres are preferably formed of starch (col. 6, line 17) or any one of gelatin, casein, dextrans, alginate, ararose, albumin, collagen, chitosan, polyvinylacetate, and hyoluronic acid esters (col. 6, lines 17-20), which gels in contact with the mucosal surface (col. 6, lines 15-16). The microspheres have a size between 10 to 100 microns (col. 6, line 13).

Illum, however, fails to teach a dry powder formulation containing microparticles formed of a drug and a polymer as defined in any of claims 1-19. The microspheres described in Illum are formed of a material described above, which does not fall within the definition of polymers defined in any of claims 1-19. Therefore, Illum does not anticipate claims 1-19 under 35 U.S.C. 102(b).

Rejections under 35 U.S.C. 103

Claims 5, 12 and 18 were rejected as obvious under 35 U.S.C. 103 over Illum in view of U.S. Patent No. 6,136,835 to Camden ("Camden"). The applicants respectfully traverse the rejection if it is applied to the claims as amended.

Camden

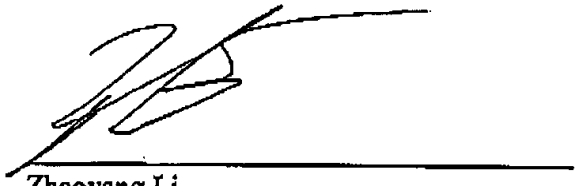
Camden describes a formulation of 2-(2,4-difluorophenyl)-1,3-bis(1H-1,-triazol-1-yl)propan-2-ol or derivatives thereof as a drug for the treatment of viral infections (col. 3, lines 20-43). The formulation may include a potentiator (col. 11, line 51). A bis-diketopiperazine derivative is listed in a large laundry list of potentiators (col. 13, line 31). A potentiator is defined as an immunomodulator that acts on the immune system (col. 11, lines 51-55). The drug can be formulated into a powder formulation, with a solid carrier, having a particle size of less than 100 microns, preferably less that about 50 microns (col. 16, lines 64-67). Solid carriers can be lactose, sucrose, gelatin, agar and bulk powders (col. 15, lines 17-19). Camden does not teach a dry powder formulation comprising the drug and the bis-diketopiperazine alone without a solid carrier. Camden does not recognize or teach the size range of 10 to 20 microns for delivery of the formulation to the desired nasal region.

Accordingly, Illum in view of Camden, failed to disclose every element of the composition and method of using the composition defined in any of claims 1-19. None of Illum and Camden teaches the desirability of **avoiding** formulations of a particle size **less than 10 microns**. Moreover, Camden teaches formulations having a particle size less than 50 microns, which encompasses formulations having a particle size in the range between 0 and 10 microns, which, as discussed above, will pass into the pulmonary region and/or mouth, resulting in a lower efficiency of drug delivery, and in the case of the delivery of antihistamine, a bitter taste of

the drug. Therefore, Illum in view of Camden, would not provide the motivation for one of ordinary skill in the art to make and use the composition defined in any of claims 1-19. Mover, none of Illum and Camden teaches making compositions having a particle size between 10 and 20 microns to cause the compositions to retain in the desired nasal mucosal region. As such, Illum in view of Camden would not lead one of ordinary skill in the art to have a reasonable expectation of success of the subject matter defined in any of claims 1-19. Moreover, Camden teaches formulations having a particle size less than 50 microns, which encompasses formulations having a particle size in the range between 0 and 10 microns, which, as discussed above, will pass into the pulmonary region and/or mouth, resulting in a lower efficiency of drug delivery, and in the case of the delivery of antihistamine, a bitter taste of the drug. This aspect of the solid formulations described in Camden teaches away from the claimed compositions and methods for using the compositions defined in any of claims 1-19. A particle size range between 10 microns and 20 microns or above is necessary for achieving nasal delivery of a drug with a higher efficiency. Illum in view of Camden fail to teach one of ordinary skill in the art with "sufficient specificity" to lead one of ordinary skill in the art to expect that nasal formulations of drug particles having a size below 10 microns would give a lower efficiency of drug delivery. Therefore, the better results (see Example 3) achieved by the formulation defined in any of claims 1-19 are unexpected to one of ordinary skill in the art (See *Ex parte Lee* 31 USPQ2d 1105 (Bd. Pat. App. & Inter. 1993). Therefore, Illum in view of Camden would not make obvious any of claims 1-19.

Allowance of claims 1-19 is therefore earnestly solicited.

Respectfully submitted,



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Dated: April 29, 2003

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CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that the enclosed Response to Office Action and all documents shown as being attached is being facsimile transmitted to the U. S. Patent and Trademark Office on the date shown below.

Date: April 29, 2003

Peggy Bailey

APPENDIX I: Marked-up C py of Claims as Pending

1. (Twice amended) A composition for the nasal administration of a drug in a dry powder form having an average particle size of between 10 and 20 microns, in a dosage formulation suitable for administration to the nasal region,

the dry powder form comprising microparticles [formed of] which comprise the drug and a [polymer or diketopiperazine] material selected from the group consisting of diketopiperazines, poly(hydroxy acids), poly(lactic acid), poly(glycolic acid) and copolymers thereof, polyanhydrides, polyesters, polyorthoesters, polyamides, polycarbonates, polyalkylenes including polyethylene and polypropylene, poly(ethylene glycol), poly(ethylene oxide), poly(ethylene terephthalate), polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, poly vinyl chloride, polystyrene, polysiloxanes, polymers of acrylic and methacrylic acids including poly(methyl methacrylate), poly(ethyl methacrylate), poly(butylmethacrylate), poly(isobutyl methacrylate), poly(hexylmethacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), polyurethanes and co-polymers thereof, celluloses including alkyl cellulose, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxy-propyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxylethyl cellulose, cellullose triacetate, and cellulose sulphate sodium salt, poly(butic acid), poly(valeric acid), poly(lactide-co-caprolactone), zein, prolamines and hydrophobic proteins, copolymers and mixtures thereof.

2. The composition of claim 1 wherein the drug is selected from the group consisting of antihistamine, vasoconstrictors, antiinflammatories and analgesics.

3. The composition of claim 2 wherein the antihistamine is selected from the group consisting of chlorpheniramine and azelastine.

4. The composition of claim 1 wherein the drug is formulated in a polymeric carrier.

5. The composition of claim 1 wherein the drug is formulated in a diketopiperazine formulation.

6. The composition of claim 1 wherein the dry powder formulation consists essentially of drug.

7. (Twice amended) A drug delivery device for nasal administration comprising

a drug in a dry powder form having an average particle size of between 10 and 20 microns, in a dosage formulation for administration to the nasal region, and

a device for delivering a measured dose of the drug to the nasal mucosa,

wherein the dry powder form comprises microparticles [formed of] which comprise the drug and a [polymer or diketopiperazine] material selected from the group consisting of diketopiperazines, poly(hydroxy acids), poly(lactic acid), poly(glycolic acid) and copolymers thereof, polyanhydrides, polyesters, polyorthoesters, polyamides, polycarbonates, polyalkylenes including polyethylene and polypropylene, poly(ethylene glycol), poly(ethylene oxide), poly(ethylene terephthalate), polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, poly vinyl chloride, polystyrene, polysiloxanes, polymers of acrylic and methacrylic acids including poly(methyl methacrylate), poly(ethyl methacrylate), poly(butylmethacrylate), poly(isobutyl methacrylate), poly(hexylmethacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate),

poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), polyurethanes and co-polymers thereof, celluloses including alkyl cellulose, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxy-propyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxylethyl cellulose, cellullose triacetate, and cellulose sulphate sodium salt, poly(butic acid), poly(valeric acid), poly(lactide-co-caprolactone), zein, prolamines and hydrophobic proteins, copolymers and mixtures thereof.

8. The device of claim 7 wherein the device is a nasal insufflator.

9. The device of claim 7 wherein the drug is selected from the group consisting of antihistamine, vasoconstrictors, antiinflammatories and analgesics.

10. The device of claim 7 wherein the antihistamine is selected from the group consisting of chlorpheniramine and azelastine.

11. The device of claim 7 wherein the drug is formulated in a polymeric carrier.

12. The device of claim 7 wherein the drug is formulated in a diketopiperazine formulation.

13. The device of claim 7 wherein the dry powder formulation consists essentially of drug.

14. (Twice amended) A method of administering a drug to the nasal region of a patient in need thereof, comprising nasally administering a dry powder form of a drug having an average particle size of between 10 and 20 microns, in a dosage formulation suitable for nasal administration,

wherein the dry powder form comprises microparticles [formed of] which comprise the drug and a [polymer or diketopiperazine] material selected from the group consisting of diketopiperazines, poly(hydroxy acids), poly(lactic acid), poly(glycolic acid) and copolymers thereof, polyanhydrides, polyesters, polyorthoesters, polyamides, polycarbonates, polyalkylenes including polyethylene and polypropylene, poly(ethylene glycol), poly(ethylene oxide), poly(ethylene terephthalate), polyvinyl alcohols, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, poly vinyl chloride, polystyrene, polysiloxanes, polymers of acrylic and methacrylic acids including poly(methyl methacrylate), poly(ethyl methacrylate), poly(butylmethacrylate), poly(isobutyl methacrylate), poly(hexylmethacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), poly(octadecyl acrylate), polyurethanes and co-polymers thereof, celluloses including alkyl cellulose, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, nitro celluloses, methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxy-propyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxylethyl cellulose, cellullose triacetate, and cellulose sulphate sodium salt, poly(butic acid), poly(valeric acid), poly(lactide-co-caprolactone), zein, prolamines and hydrophobic proteins, copolymers and mixtures thereof.

15. The method of claim 14 wherein the drug is selected from the group consisting of antihistamine, vasoconstrictors, antiinflammatories and analgesics.

16. The method of claim 14 wherein the antihistamine is selected from the group consisting of chlorpheniramine and azelastine.

17. The method of claim 14 wherein the drug is formulated in a polymeric carrier.

18. The method of claim 14 wherein the drug is formulated in a diketopiperazine formulation.

19. The method of claim 14 wherein the dry powder formulation consists essentially of drug.